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MOLECULAR CLONING OF THE HUMAN CRH2 RECEPTOR SUBTYPE. C.Z. Pratt, J.M. Cook, A.A. Speirs, D.D. Auperin, J.R. de Wet. Department of Molecular Sciences, Central Research Division, Pfizer Inc, Groton, CT 06340.

We have cloned and sequenced a novel human cDNA that encodes a member of the corticotropin-releasing hormone (CRH) receptor family. A portion of the cDNA was isolated from human brain and skeletal muscle using the polymerase chain reaction and oligonucleotide primers of degenerate sequence derived from the amino acid sequence of the human CRH receptor. The remaining N-terminal coding sequence of the cDNA was obtained by 5' RACE (rapid identification of cDNA ends) using human heart total RNA as template. The 3' region of the sequence was determined by analyzing clones isolated from a bacteriophage lambda human genomic DNA library. The nucleotide sequence predicts a 411 amino acid protein with a 94%, 85% and 70% identity to the amino acid sequences of the rat CRH2A, the rat CRH2B and the human CRH1A receptors, respectively, and thus is most likely the human homologue of the CRH2A receptor. Partial analysis of human genomic clones of the CRH2A receptor shows that the gene is interrupted by several introns and has a structure that is similar to that of the related mouse parathyroid hormone, mouse growth hormone, and porcine calcitonin receptor genes.

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CENTRAL INTERACTIONS OF CORTICOTROPIN-RELEASING FACTOR (CRF) WITH OTHER HYPOTHALAMIC NEUROPEPTIDES - ROLE IN CARDIOVASCULAR CONTROL. R. Richter, D. Michl. Institute of Molecular Pharmacology, D-10315 Berlin, Germany.

Chronic overflow of CRF, a 41 amino acid peptide, seems to be associated with maladaptive and pathological consequences such as hypertension. There is evidence that a number of neuropeptides, which coexist with CRF in the hypothalamus, are involved in regulation of CRF release by different mechanisms. In this study we test the hypothesis whether the neuropeptides substance P (SP), NPY and ANP exert an inhibitory control on CRF-evoked cardiovascular responses.

We measured the cardiovascular responses (mean arterial blood pressure [MAP] and heart rate [HR] to centrally (icv) injected CRF (0.2 and 1 nmol) in conscious Wistar rats without and after pretreatment with the neuropeptides. In order to compare the inhibitory potency of the neuropeptides with that of the competitive CRF receptor antagonist, α-helical CRF(9-41), the respective agonist:antagonist molar ratio was calculated.

1. After icv injection of SP (0.025-0.25 nmol) there was a dose-dependent attenuation of the CRF induced increase in MAP (36% to 73%) and HR (34% to 73%) ($p<0.01$). The inhibitory effect was prevented by pretreatment with the selective NK1 receptor antagonist CP-96,345.
2. While significant inhibition of the CRF-evoked cardiovascular response required an agonist:antagonist molar ratio of 1:10 (α-hel CRF[9-41]), inhibition by SP was obtained with a 1:0.025 molar ratio of CRF:SP.
3. Icv injection of ANP (0.05-2.5 nmol) caused a dose-dependent increase in MAP and HR, while NPY (0.1-3 nmol) evoked a dose-dependent biphasic cardiovascular response: initial hypotension and bradycardia was followed by a transient increase in MAP and HR. However, the inhibitory potency of ANP and NPY by blocking the CRF actions was less pronounced.
4. Compared with the CRF antagonist, α-hel CRF(9-41), the inhibitory potency of the peptides followed the order: SP » ANP » NPY » α-hel CRF(9-41).

The results demonstrate marked differences in the ability of the neuropeptides SP, ANP and NPY to inhibit CRF-evoked cardiovascular responses, resulting from activation of multiple CNS sites.

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